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DOI:
10.1016/j.ijcard.2014.11.101

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Sardar, P, Chatterjee, S, Lavie, CJ, Giri, JS, Ghosh, J, Mukherjee, D & Lip, GYH 2015, 'Risk of major bleeding in different indications for new oral anticoagulants: insights from a meta-analysis of approved dosages from 50 randomized trials', *International Journal of Cardiology*, vol. 179, pp. 279-287. https://doi.org/10.1016/j.ijcard.2014.11.101

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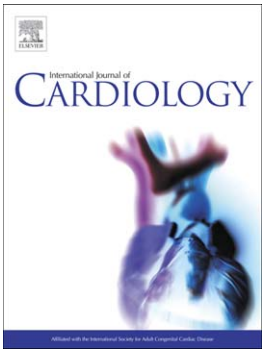

Risk of Major Bleeding in Different Indications for New Oral Anticoagulants: Insights from a Meta- Analysis of Approved Dosages from 50 Randomized Trials

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PII: S0167-5273(14)02245-1
DOI: doi: 10.1016/j.ijcard.2014.11.101
Reference: IJCA 19258

To appear in: *International Journal of Cardiology*

Received date: 16 December 2013
Revised date: 17 September 2014
Accepted date: 10 November 2014

Please cite this article as: Sardar Partha, Chatterjee Saurav, Lavie Carl J., Giri Jay S., Ghosh Joydeep, Mukherjee Debabrata, Lip Gregory Y.H., Risk of Major Bleeding in Different Indications for New Oral Anticoagulants: Insights from a Meta- Analysis of Approved Dosages from 50 Randomized Trials, *International Journal of Cardiology* (2014), doi: 10.1016/j.ijcard.2014.11.101

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Risk of Major Bleeding in Different Indications for New Oral Anticoagulants: Insights from a Meta- Analysis of Approved Dosages from 50 Randomized Trials

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Competing interests: GYHL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi; no other relationships or activities that could appear to have influenced the submitted work.

Funding: None

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Word Count: 2998

Key words: bleeding; new oral anticoagulants; rivaroxaban; dabigatran; apixaban; meta-analysis

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Background: A meta-analysis was performed to evaluate the risk of major bleeding with the use of New Oral Anticoagulants (NOACs).

Methods: Randomized controlled trials (RCTs) comparing NOACs (rivaroxaban, dabigatran, apixaban, edoxaban and darexaban) with comparators were selected.

Results: Fifty trials included 155,537 patients. Pooled analysis of all NOACs for all indications together demonstrated no significant difference between NOACs and comparators for risk of major bleeding (Odds Ratio [OR] 0.93, 95% CI 0.79- 1.09). Pooled analysis also showed, NOACs caused significantly less major bleeding compared to vitamin K antagonists (VKA) (0.77, 0.64- 0.91). Analysis for individual NOACs showed risk of major bleeding were not different with rivaroxaban, apixaban or dabigatran compared to pharmacologically active comparators or VKA. Indication specific analysis showed, NOACs were associated with significantly higher major bleeding after hip surgery (1.43, 1.02 -1.99), in patients with acute coronary syndrome (ACS), (compared against placebo) (2.89, 2.01-4.14), and for medically ill patients (2.79, 1.69-4.60). For the treatment of acute venous thromboembolism (VTE) or pulmonary embolism (PE), NOACs were associated with significantly less bleeding (0.63, 0.44-0.90). No significant difference was found between NOACs and comparators in treatment of atrial fibrillation and for extended treatment of VTE.

Conclusions: Risk of major bleeding with new oral anticoagulants varies with their indication for use. New agents may be associated with comparatively less major bleeding compared to VKA. NOAC may increase the risk of major bleeding after hip surgery, ACS and acute medically ill patients; but may be associated with less bleeding in treatment of acute VTE/PE.

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Key words: Bleeding; new oral anticoagulants; rivaroxaban; dabigatran; apixaban; meta-analysis

Introduction

New oral anticoagulant agents (NOACs) have been developed in recent years for use in different indications. The newer agents have specific advantages over conventional anticoagulants, including rapid onset of action, predictable therapeutic effect, and limited interactions with other drugs (1). The two groups of NOACs include the factor Xa (FXa) inhibitors (eg. rivaroxaban, apixaban, edoxaban and darexaban) and direct thrombin inhibitors (DTIs, eg. dabigatran and ximelagatran) (1).

Rivaroxaban is approved in the United States and Europe for thromboprophylaxis after orthopedic surgery, treatment of venous thromboembolism (VTE), and for stroke prevention in patients with atrial fibrillation (AF); in Europe rivaroxaban has been recently approved for acute coronary syndrome (ACS) (1-4). Apixaban is approved in Europe for patients with atrial fibrillation and for thromboprophylaxis after orthopedic surgery and in the United States apixaban recently received approval for patients with atrial fibrillation only (5, 6). Ximelagatran is no longer available because of reports of liver toxicity (1). Dabigatran is approved in the United States for stroke prevention in non-valvular AF, and in Europe this drug received additional approval for thromboprophylaxis after orthopedic surgery (1, 7, 8). Other new drugs, edoxaban and darexaban have been evaluated in phase II trials (1,9).

However, the major disadvantage of the NOACs is the lack of specific antidotes that would reverse their action in a patient with major bleeding (1, 10, 11). Also, no reliable laboratory tests are available to monitor the effects of these agents (10, 11).Thus, there is some concern regarding the risk of major bleeding with these new agents, which on occasion can even be life

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threatening (1,10,11). No major study or systematic review focusing only on comparative bleeding risk with these drugs has been published. At the same time there is no previous or ongoing, head-to-head trial among these new agents, although indirect comparisons provide some insights into some differences in safety endpoints (12).

We performed a systematic review and meta-analysis of published randomized clinical trials to evaluate the risk of major bleeding with new oral anticoagulants.

Methods

We systematically searched the published literature for trials comparing any of the new oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban and darexaban) with conventionally used medications/anticoagulants among various indications for anticoagulation.

Data Sources and Searches

We electronically searched PubMed, Cochrane CENTRAL, EMBASE, EBSCO, Web of Science and CINAHL databases for English language, peer-reviewed publications of NOACs from January 2001 through October 31, 2013. Further details of the search strategy are mentioned in the Online-only Data Supplement Appendix.

Study Selection

The included studies were randomized clinical trials; the trials evaluated any new oral anticoagulants including dabigatran, rivaroxaban, apixaban, edoxaban or darexaban; the

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comparator was any active pharmacologic agents or placebo and major bleeding outcome was reported. We included studies with commonly evaluated indications for newer anticoagulants' use in randomized clinical trials: thromboprophylaxis after hip surgery, thromboprophylaxis after knee surgery, treatment of acute VTE or pulmonary embolism (PE), extended treatment of venous thromboembolism, prevention of embolism/stroke in atrial fibrillation (AF), acute coronary syndrome (ACS) and thromboprophylaxis in medically ill patients. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs (13) was used as a reference method for this study.

Data Extraction and Quality Assessment

Two authors (PS, SC) reviewed the trials, ensured that they met inclusion criteria and abstracted the data; disagreements were resolved by discussion with other authors. Risk for bias was assessed by the procedures suggested by the Cochrane Handbook of Systematic Reviews (14).

Data Synthesis and Analysis

The outcome of interest was major bleeding events in the study group and the comparator group. For trials that evaluated 2 or more doses of NOACs, we used the outcome related to the approved total daily dose/closely related dose of the experimental drug for our analysis. For phase II trials we used the dose, which was subsequently tested in phase III trials, and when only phase II data was available, we chose the most frequently used dose of those drugs (for specific indications) in all trials with acceptable efficacy profile. (Details in Online-only Data Supplement Appendix).

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Statistical analysis

We performed pooled comparisons between dabigatran, rivaroxaban, apixaban, edoxaban and darexaban versus comparators on safety analysis population. In this analysis, Review Manager Version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008, Copenhagen) was used. We calculated odds ratio (OR) estimates and associated 95% confidence intervals (CIs) for each of the oral anticoagulants and for each indication of use. We assessed the heterogeneity using the Cochran Q test and the Higgins I^2 statistic . We calculated the total event rates calculated by summing up all events across all trials and dividing by the total number of patients across all trials. For our main analysis random effects models described by Der-Simonian and Laird was used. For studies using dissimilar agents in the control group, the random-effects model was applied. For sensitivity analysis, we used fixed effects model described by Mantel and Haenszel. We calculated prediction intervals for major bleeding using a random effect model (DerSimonian and Laird). Indirect comparisons between these drugs (with indication specific conventional drugs as a common comparator) were also done. We used Stata 11.2 (StataCorp LP, College Station, Texas) software for indirect comparisons [Bucher's method] (15). Small study effects (publication bias) was assessed graphically by evaluating the standard error and the effect size in the funnel plots.

Results

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A total of 5742 reports were identified by our electronic database search (Figure 1). Finally, 50 trials involving a total 155,537 patients in safety analysis groups met our inclusion criteria and were selected for the present analysis (Online-only Data Supplement Appendix).

Characteristics of included studies

The included trials were conducted for different indications for anticoagulation therapy; thromboprophylaxis after hip surgery (12 studies), thromboprophylaxis after knee surgery (9 studies), treatment of acute VTE/PE (8 studies), treatment of patients with ACS (6 studies), prevention of stroke/embolic events in patients with AF (10 studies), extended treatment of VTE (4 studies), and thromboprophylaxis in medically ill patients (2 studies). The BISTRO II trial included both hip and knee surgery patients, we used the published data for separate analysis (16). The numbers of included trials appraising rivaroxaban, apixaban, dabigatran, edoxaban and darexaban were eighteen, twelve, twelve, five and three respectively.

Most of the studies used the International Society on Thrombosis and Hemostasis (ISTH) criteria in documenting major bleeding, though there were inter trial variation/modification in the definition (Online-only Data Supplement Appendix). In the ACS trials, Thrombolysis In Myocardial Infarction (TIMI) major bleeding events were included in the analysis. In acute VTE studies patients received treatment for 3 or 12 months, and in "extended VTE treatment" studies patients received additional 6 to 12 months of treatment. For the studies with acutely ill medical patients, NOAC was given for 30-35 days versus LMWH for 6-14 days followed by placebo for the rest of the period.

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Inter-rater reliability between the reviewers in the assessment of risk of bias was good with a kappa statistic of 0.85. A total of 33 studies showed low risk of bias, and among them 25 studies evaluated NOACs against active comparators.

The pooled effect estimate according to Study Drug/ Comparator Drug (NOACs versus comparators)

Pooled analysis of all NOACs together for all indications of anticoagulation showed, there was no significant difference between NOACs and pharmacologically active comparators for the risk of major bleeding [Odds ratio (OR) 0.93, 95% Confidence Interval (CI) 0.79- 1.09, I^2=56%], 2.4% with NOACs versus 2.7% with pharmacologically active comparators (Figure 2). Sensitivity analysis including trials with only low risk of bias also showed similar result (Online Supplement). Newer agents caused statistically significant less major bleeding compared to vitamin K antagonists (OR 0.77, 95% CI 0.64- 0.91, I^2=61%, p=0.003), 3.3% versus 3,9%. A similar result was found for pooled analysis with three available/approved NOACs (rivaroxaban, dabigatran, apixaban) (OR 0.76, 95% CI 0.63- 0.92, I^2=67%, p=0.005), 3.6% versus 4.2% (Figure 3).

Direct comparison analysis for individual NOACs showed, when considering each NOAC separately, there was on average no evidence of an effect of any of these relative to pharmacologically active agents; for rivaroxaban (OR 1.10, 95% CI 0.77- 1.58, I^2=57%; 2.4% with rivaroxaban versus 2.3% with active agents), apixaban (OR 0.81, 95% CI 0.56- 1.119, I^2=67%; 1.9% versus 2.5%) or dabigatran (OR 0.96, 95% CI 0.76- 1.20, I^2=20%; 3.8 % versus 4.0%) (Table 1). Similar findings with these three newer agents were also observed for separate analysis against vitamin K antagonists and low molecular weight heparin (LMWH) (Table 1).

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Indirect comparisons between individual NOACs did not show any major differences between rivaroxaban, dabigatran, apixaban, edoxaban and darexaban for the risk of major bleeding (Online-only Data Supplement Appendix).

The pooled effect estimate according to indications

The pooled effect estimate for major bleeding complications with NOACs varied considerably across different indications of anticoagulation therapy.

(a) <u>Thromboprophylaxis after hip surgery</u> (12 RCTs, 18627 patients):

For the prevention of venous thromboembolism after hip surgery, there was a statistically significant higher risk of major bleeding with use of NOACs compared to LMWH (OR 1.43, 95% CI 1.02 -1.99; I^2=0%, p=0.04) (Figure 4). Among 9262 patients there were 87 incidences (0.9%) of major bleeding with NOACs, whereas there were 61 incidences (0.6%) of major bleeding with LMWH among 9365 patients. When direct comparison analysis was done separately with pooled effects estimate of individual NOACs (rivaroxaban, dabigatran, apixaban, edoxaban and darexaban) versus LMWH, all the NOACs showed an increased trend towards major bleeding (Table2).

(b) <u>Thromboprophylaxis after Knee Surgery</u> (9 RCTs, 15840 patients):

For thromboprophylaxis after knee surgery, there was a trend towards less bleeding with NOACs but the results did not reach statistical significance (OR 0.88, 95% CI 0.55-1.39, I^2=30%), 0.7% versus 0.9% (Figure 4). Apixaban individually caused significantly less bleeding in comparison to LMWH, when pooled analysis was done with phase III trials. But pooled effects of individual NOACs were not different from that of LMWH (Table 2).

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(c)Extended Treatment of Venous Thromboembolism (4 RCTs, 7864 patients)

Major bleeding with NOACs was not different compared to placebo (OR 1.87, 95% CI 0.19-17.96, I^2=61%), 0.3% versus 0.1% (Figure 4 and Table 2).

(d) Acute Venous Thromboembolism/Pulmonary embolism (8 RCTs, 25161 patients) :

In treatment of acute VTE/PE, NOACs caused significantly less bleeding compared to conventional treatment (OR 0.63, 95% CI 0.44-0.90, I^2=48%, p=0.01), 1.1% versus 1.7% (Figure 5). Compared to VKA, the most robust evidence (from four RCTs) was found with rivaroxaban.

(e) Atrial Fibrillation (10 RCTs, 52539 patients)

In patients with Atrial Fibrillation, bleeding risk with NOACs versus VKA/aspirin was not statistically different (OR 0.89, 95% CI 0.74-1.06), 4.5% versus 5.1%. There was considerable heterogeneity among the studies (I^2=62%; p=0.01) (Figure 5). In our direct comparison analysis, pooled effects estimate of individual NOACs were not different from that of the comparator drugs (Table 2).

(f) Acute coronary syndrome (6 RCTs, 21107 patients)

Uses of NOACs were associated with a high risk of major bleeding in patients with Acute Coronary Syndrome (OR 2.89, 95% CI 2.01-4.14, I^2=-0%, p<0.001), 1.2% versus 0.4%, (Figure 5). Individually, all three commonly-used NOACs dabigatran, rivaroxaban and apixaban caused more bleeding compared to placebo, results with rivaroxaban and apixaban were statistically significant (Table 2).

(g) Thromboprophylaxis in Medically Ill Patients (2 RCTs, 14399 patients)

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Newer agents caused more major bleeding compared to LMWH/placebo after 30 days treatment period (OR 2.79, 95% CI 1.69-4.60, I^2=0%, p<0.001), 0.8% versus 0.3%; however the CIs were wide (Figure 5 and Table 2). Separate analysis showed NOAC caused higher bleeding compared to initial LMWH therapy and also during "placebo comparison period".

Unlike the effects estimate according to the study drugs/comparator drugs, the majority of the results for indication-wise effects estimate showed insignificant heterogeneity.

Small study effects

We did not find any evidence of significant bias due to "small study effects" for our analyses with examination of funnel plots (Online supplement figure).

Discussion

Our pooled analysis showed that, when compared against pharmacologically active drugs or placebo (in case of ACS), the risk of major bleeding overall was not significantly different with NOACs. Nonetheless, the newer agents may even cause lower major bleeding compared to VKA. Second, this meta-analysis identified important differences in major bleeding events with newer oral anticoagulants in different indications. Differences also exist with the type of surgical procedure; NOACs caused statistically significant higher rates of major bleeding compared to LMWH, when used after hip surgery. On the other hand there was a trend towards less bleeding with NOACs after knee surgery. For non-surgical indications, in treatment of acute VTE, NOACs showed consistently lower risk of bleeding, compared to VKA. In patients with atrial fibrillation and those undergoing extended treatment for VTE, NOACs and comparator drugs

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showed no statistically significant differences in major bleeding. In patients with ACS and thromboprophylaxis in medically ill patients, NOACs caused more bleeding. For different indications of anticoagulation, no major difference in bleeding was found between any individual new agent (NOAC) versus comparator drugs in pooled effect estimates.

Importantly, this study only analyzed data using approved doses of individual agents or commonly used doses in phase III trials. Thus, the results of our analysis are more likely to simulate real-life risk of major bleeding, assuming agents are used as in their respective clinical trials.

The results of our meta-analysis perhaps reflect the complex nature of the coagulation cascade and multiple factors influencing it, as well as different dose regimens and concomitant comorbidities and drug therapies (10, 11, 17, 18). As mentioned earlier, different dose regimens of NOAC have been used for different indications and NOACs have been evaluated against different comparators. This might explain some of the differences in risk of bleeding with NOAC in different indication of use. For instance, excess bleeding with NOACs in ACS might be related to co-interaction with anti-platelet therapy. Additionally, the comparison group in ACS trials was placebo (19, 20). However, the increased risk of major bleeding with newer agents might attenuate their ischemic benefits in patients with ACS (19).

Higher rate of major bleeding in hip surgery but not in knee surgery may be related to the longer duration of NOAC therapy and higher baseline risk in subjects undergoing hip surgery (21, 22). Another point to consider is that comparator groups in most of the trials of hip surgery received 40 mg daily LMWH (approved dose in Europe), while the majority of the comparator groups in knee surgery received 30 mg twice daily (i.e. total 60 mg daily; approved dose in North

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America). Again, higher bleeding with NOACs in medically ill patients may be related to the baseline risks of the subjects, although 'acute medically ill' represents a heterogeneous group of patient conditions (23, 24).

A previous meta-analysis (20), reported that collectively, the risk of major bleeding complications was higher for rivaroxaban, and lower for apixaban and dabigatran; however, this analysis was affected by considerable heterogeneity. On the other hand, our pooled analysis did not show any significant difference with individual NOACs and pharmacologically active comparators. Our indirect comparison analysis also did not show any major differences between the individual NOAC; for all indications together and also for separate analysis for individual indications. When we pooled the data according to the indications of anticoagulation (instead of according to individual drugs), focusing on approved doses of the individual drugs available, most of our findings showed no marked heterogeneity. Thus, when considering the bleeding risk of NOACs, examining the specific indication for anticoagulation may be more relevant than looking for individual drug effects among all indications.

A recent meta-analysis did not find any statistically significant interaction of the type of surgery (total hip or knee replacement) for clinically relevant bleeding (25). Another meta-analysis pooled the data of both knee and hip surgery and reported that use of factor Xa inhibitors increased the risk of major bleeding (26). On the contrary, in our analysis, NOACs were associated with significantly higher risk of bleeding with hip surgery, but not in knee surgery. Thus, the risk of bleeding may possibly be more related to type of surgery, baseline risk of subjects, or comparators than type of NOACs used. Despite recent reports suggested the

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possibility of higher bleeding with newer agents (1, 20), our findings that major bleeding is actually lower with NOACs may justify use of NOACs in patients with high risk of bleeding with VKA. Of note, we did not find any specific advantage of any individual NOACs against VKA.

Bleeding risk is the major limitation with new anticoagulant therapy, as there is no reliable reversal agent. At the same time the NOACs have definite advantage in term of efficacy and convenience in long term use over conventional anticoagulants like VKA/heparin (1,10, 11, 27). In this situation prediction of bleeding according to the indication of anticoagulation and careful patient as well as specific newer agent selection is the only acceptable option to optimize the bleeding risk. However, inter-agent comparisons of this kind can only be considered to be hypothesis generating and provide the basis for large head to head randomized controlled trials.

Limitations

We recognize differences in study population, protocol, intervention and duration of follow-up across the included trials. Widened confidence intervals for few agents and indications make interpretation difficult, especially in cases of edoxaban and darexaban. Our results are estimates of average effects, and a degree of unexplained statistical heterogeneity around these averages is present. Definitions of major bleeding varied considerably in the studies, which was very difficult to adjust in the pooled analysis. All included studies reported major bleeding as a composite outcome, and components of the composite outcome ranging from severe intracranial bleeding to comparatively less important outcomes such as decrease in hemoglobin level of 2

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g/dl, which make interpretation of the combined results challenging. Effects of older age and impaired renal function on bleeding risks could not be pooled due to non-availability of data.

Conclusion

NOACs may be related to higher risk of bleeding in hip surgery, acute coronary syndrome and thromboprophylaxis in medically ill patients, but causes less bleeding in patients with acute venous thromboembolism (VTE) or pulmonary embolism (PE). In patients with atrial fibrillation, knee surgery and extended treatment of venous thromboembolism, NOACs may not necessarily be associated with increased bleeding risk when used in approved doses. Collectively and individually the NOACs may cause equal or even less major bleeding when compared to vitamin K antagonists.

Contributors

PS and SC had the initial concept and they designed the study. PS and SC reviewed the published work and extracted data, with guidance from DM, CJL, JG and GYL. SC, and PS did the statistical analysis. All authors participated in data interpretation (PS, SC, CJL, JSG, JG, DM and GYL). PS wrote the first draft of the report, modified initially by SC, and subsequently by all other authors (DM, CJL, JG, JSG and GYL). All authors commented on the draft and approved the final version.

Acknowledgement: Partha Sardar and Saurav Chatterjee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests: GYHL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi; no other relationships or activities that could appear to have influenced the submitted work.

References

1. Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157:796-807.
2. U.S. Food and Drug Administration. FDA News Release: Nov. 2, 2012. FDA expands use of Xarelto to treat, reduce recurrence of blood clots. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm326654.htm. Accessed March 12, 2013.
3. European Medicines Agency. Public assessment report for Xarelto. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Summary_for_the_public/human/000944/WC500057109.pdf. Accessed March 12, 2013.
4. National Institute for Health and Clinical Excellence Guideline. Venous thromboembolism - rivaroxaban (TA170). http://guidance.nice.org.uk/TA170. Accessed March 12, 2013.
5. European Medicines Agency. Public assessment report for Eliquis. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/002148/WC500107773.pdf. Accessed March 12, 2013.
6. Prasad V, Kaplan RM, Passman RS. New frontiers for stroke prevention in atrial fibrillation. Cerebrovasc Dis. 2012;33:199-208.
7. Beasley BN, Unger EF, Temple R. Anticoagulant options--why the FDA approved a higher but not a lower dose of dabigatran. N Engl J Med. 2011;364:1788-90.

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8. European Medicines Agency. Public assessment report for Pradaxa. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Summary_for_the_public/human/000829/WC500041060.pdf . Accessed March 12, 2013.
9. Miller CS, Grandi SM, Shimony A, et al. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012;110:453-60.
10. Kazmi RS, Lwaleed BA. New anticoagulants: how to deal with treatment failure and bleeding complications. Br J Clin Pharmacol. 2011;72:593-603.
11. Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012;119:3016-23.
12. Rasmussen LH, Larsen TB, Graungaard T, et al. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ. 2012;345:e7097. doi: 10.1136/bmj.e7097.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009; 18; 151:W65-94.
14. Higgins JPT, Altman DG, Sterne JAC, eds. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). Available at: http://www.cochrane-handbook.org.
15. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epid. 1997; 50:683–91.
16. Eriksson BI, Dahl OE, Büller HR, et al; BISTRO II Study Group. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. J Thromb Haemost. 2005 ;3:103-11.
17. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573-9.
18. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost. 2012;108:217-24.
19. Komócsi A, Vorobcsuk A, Kehl D, et al. Use of New-Generation Oral Anticoagulant Agents in Patients Receiving Antiplatelet Therapy After an Acute Coronary Syndrome: Systematic Review and Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2012 ;172:1537-45.

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20. Mak KH. Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials. BMJ Open. 2012 Oct 6;2(5). pii: e001592.

21. Deitelzweig SB, McKean SC, Amin AN, et al. Prevention of venous thromboembolism in the orthopedic surgery patient. Cleve Clin J Med. 2008;75 Suppl 3:S27-36.
22. Sobieraj DM, Lee S, Coleman CI, et al. Prolonged versus standard-duration venous thromboprophylaxis in major orthopedic surgery: a systematic review. Ann Intern Med. 2012 ;156:720-7.

23. Cohen AT, Spiro TE, Büller HR, et al; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368:513-23.
24. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al; ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365:2167-77.
25. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, et al. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ. 2012;344:e3675.
26. Neumann I, Rada G, Claro JC, et al. Oral direct Factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. Ann Intern Med. 2012;156:710-9.
27. De Caterina R, Husted S, Wallentin L, et al; Coordinating Committee. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol. 2012;59:1413-25.

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Figure Legends

Figure 1: Search strategy and study selection as per PRISMA checklist.

Figure 2: Forest plot comparing all new oral anticoagulants versus pharmacologically active agents for risk of major bleeding

Figure 3: Forest plot for major bleeding comparing three approved/available new oral anticoagulants (rivaroxaban, dabigatran and apixaban) versus vitamin K antagonists.

Figure 4: Risk of major bleeding with NOACs versus comparators, for thromboprophylaxis after hip surgery (A), for thromboprophylaxis after knee surgery (B), and for extended treatment of venous thromboembolism(C)

Figure 5: Risk of major bleeding with NOACs versus comparators, for treatment of acute VTE/PE (A), for Atrial Fibrillation (B), for Acute Coronary Syndrome (C) and for thromboprophylaxis in medically ill patients(D)

Table 1: Analysis of pool effect estimates of NOACs versus comparators, according to study and comparator drugs.

Table 2: Direct comparison analysis of pool effect estimates of individual NOACs versus comparator drugs, according to different indications.

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Table 1: Analysis of pool effect estimates of NOACs versus comparators, according to study and comparator drugs.

	Study drug-incidence/total **Comparators-incidence/total**	**Odds Ratio (95% CI)**	**No of Study**
All NOACs vs active comparators	1544/64716 1733/64706	0.93 [0.79, 1.09], I^2=56%	42 studies
All NOACs vs active comparators (phase III trials)	1512/62126 1710/62096	0.90 [0.76, 1.07]. I^2=69%	24 studies
All NOACs vs Vitamin K antagonist	1339/40364 1580/40192	0.77 [0.64, 0.91], I^2=61%	19 studies
All NOACs vs LMWH	205/24352 153/24514	1.32 [0.98, 1.78], I^2=34%	23studies
3 Available NOACs vs active comparator	1485/59786 1662/59756	0.94 [0.79, 1.12], I^2=61%	35 Studies
3 Available NOACs vs Vitamin K antagonist	1283/35801 1511/35616	0.76 [0.63, 0.92]I^2=67%	15 studies
3 Available NOACs vs LMWH	202/23985 151/24140	1.32 [0.96, 1.81], I^2=40%	20 studies
3 Available NOACs vs LMWH(Excluding MAGELLAN &ADOPT)	144/16804 130/16922	1.12 [0.84, 1.51], I^2=19%	18 studies
Dabigatran vs active comparators	500/13031 526/12894	0.96 [0.76, 1.20], I^2=20	10 studies
Dabigatran vs Vitamin K antagonist	432/8946 470/8783	0.83 [0.62, 1.12], I^2=33%	4 studies

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Dabigatran vs LMWH	68/4085 56/4111	1.23 [0.86, 1.77], I^2=0%	5 studies
Rivaroxaban vs active comparators	537/22725 525/22857	1.10 [0.77, 1.58], I^2=57%	15 studies
Rivaroxaban vs Vitamin K antagonist	464/12084 490/12100	0.79 [0.55, 1.13], I^2=54%	6 studies
Rivaroxaban vs LMWH	73/10641 35/10757	2.05 [1.29, 3.24] , I^2=6%	9 studies
Rivaroxaban vs LMWH (excluding MAGELLAN trial)	30/6644 20/6756	1.56 [0.86, 2.83], I^2=0%	8 studies
Apixaban vs all active comparators	448/24030 611/24005	0.81 [0.56, 1.19], I^2=67%	10 studies
Apixaban vs Vitamin K antagonist	387/14771 551/14733	0.66 [0.40, 1.09], I^2=70%	5 studies
Apixaban vs LMWH	61/9259 60/9272	1.08 [0.54, 2.12], I^2=63%	5 studies
Apixaban vs LMWH (excluding ADOPT trial)	46/6075 54/6055	0.84 [0.43, 1.62], I^2=53%	4 studies

Bold signifies statistically significant result

ADOPT=Apixaban Dosing to Optimize Protection from Thrombosis trial; CI =Confidence Interval;

LMWH=Low molecular weight heparin.

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Table 2: Direct comparison analysis of pool effect estimates of individual NOACs versus comparator drugs, according to different indications

Hip Surgery	**Odds Ratio (95% CI)**	**Treatment of acute VTE/PE**	**Odds Ratio (95% CI)**
Dabigatran vs. comparator	1.49 [0.96, 2.34], I^2=0%, 3 studies	Dabigatran vs. comparator	0.82 [0.45, 1.50] , I^2=NA, 1study
Rivaroxaban vs. comparator	1.71 [0.67, 4.39] , I^2=0%, 5 studies	Rivaroxaban vs. comparator	**0.57 [0.39, 0.83]** , I^2=0%, 4 studies
Apixaban vs. comparator	1.22 [0.65, 2.28] , I^2=NA, 1 study	Apixaban vs. comparator	2.57 [1.03, 6.37] , I^2=0%, 1 study
Edoxaban vs. comparator	3.05 [0.12,75.47] , I^2=NA, 1 study	**Acute Coronary Syndrome**	
Darexaban vs. comparator	0.21 [0.01, 4.41] , I^2=NA, 2 studies	Dabigatran vs. comparator	1.07 [0.07, 17.16] , I^2=NA, 1 study
Knee Surgery		Rivaroxaban vs. comparator	**3.45 [2.07, 5.76]** , I^2=NA, 1 study
Dabigatran vs. comparator	0.85 [0.45, 1.58] , I^2=0%, 3 studies	Apixaban vs. comparator	**2.58[1.53, 4.35]** , I^2=0%, 2 studies
Rivaroxaban vs. comparator	1.40 [0.55, 3.55] , I^2=23%, 3studies	Darexaban vs. comparator	0.69 [0.03, 17.08] , I^2=NA, 1 study
Apixaban vs. comparator	0.69 [0.30, 1.61] ,	**Atrial Fibrillation**	

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	I^2=46%, 3studies		
Extended treatment of VTE		Dabigatran vs. comparator	0.94 [0.81, 1.08] , I^2=NA, 2 studies
Dabigatran vs. comparator	0.96 [0.13,6.97] , I^2=51%, 2 studies	Rivaroxaban vs. comparator	1.02 [0.88, 1.17] , I^2=0%, 2 studies
Apixaban vs. comparator	0.37[0.08,1.67], I^2=NA, 1 study	Apixaban vs. comparator	0.82 [0.55, 1.24] , I^2=55%, 3studies
Acutely Ill Medical Patients		Edoxaban vs. comparator	0.25 [0.03, 2.29] , I^2=0%, 3 studies
Rivaroxaban vs. comparator	**2.89[1.60,5.21]** , I^2=NA, 1 study		
Apixaban vs. comparator	**2.53[0.98,6.54]** , I^2=NA, 1 study		

Bold signifies statistically significant result

CI =Confidence Interval; NA=not applicable; PE= Pulmonary embolism; VTE= Venous Thromboembolism.

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Fig. 1. Search strategy and study selection as per PRISMA checklist.

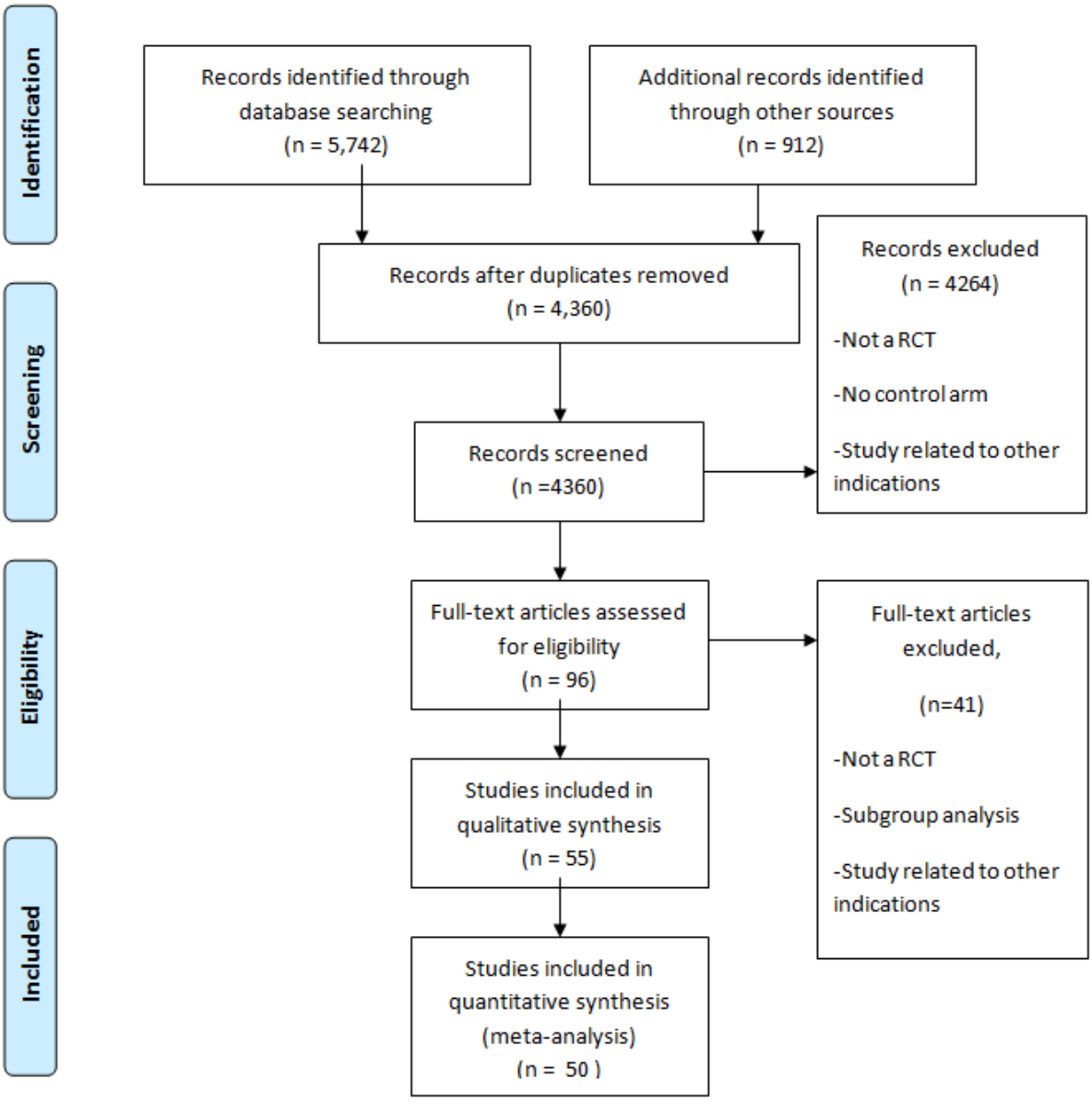

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Fig. 2

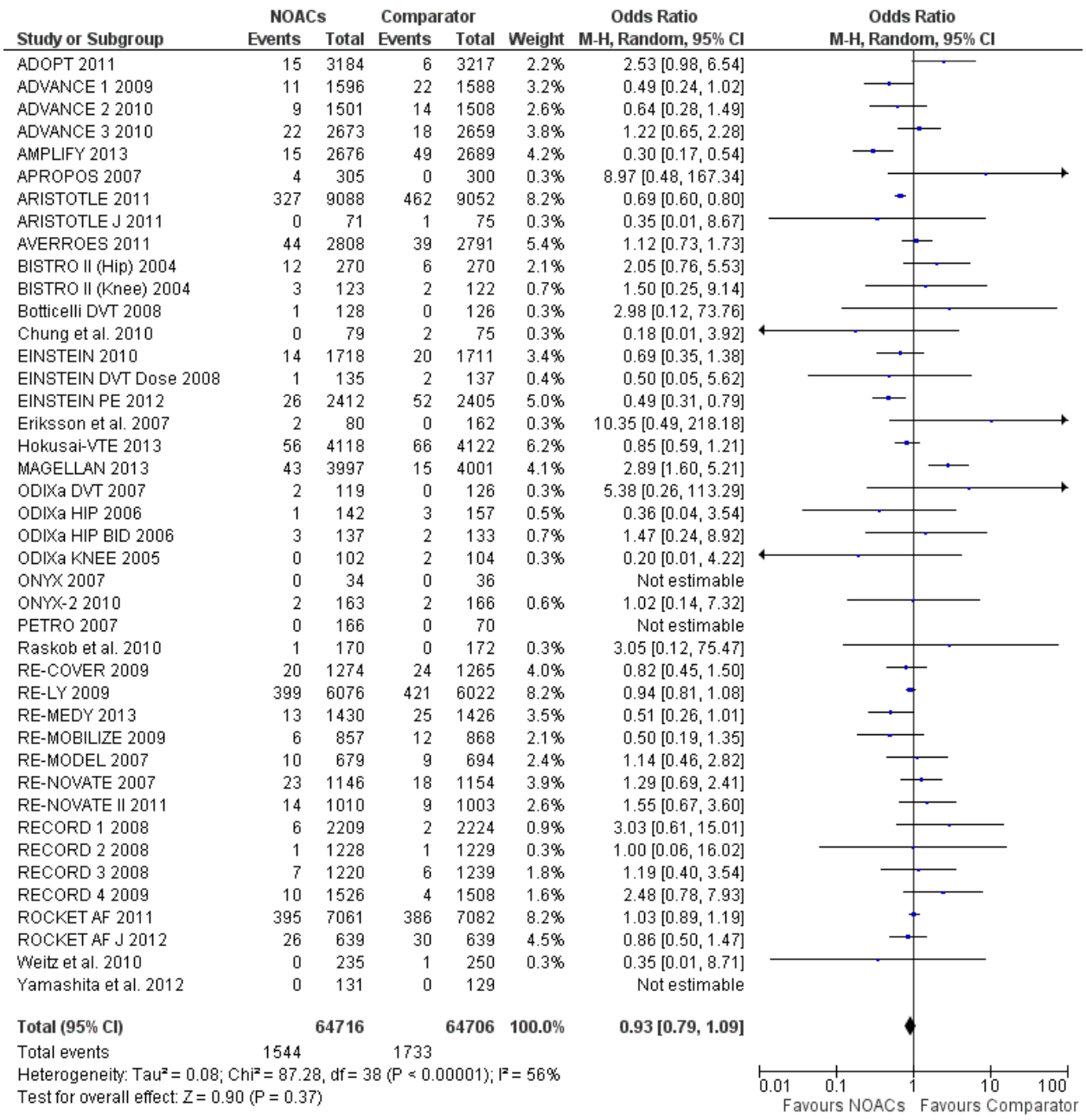

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Fig. 3

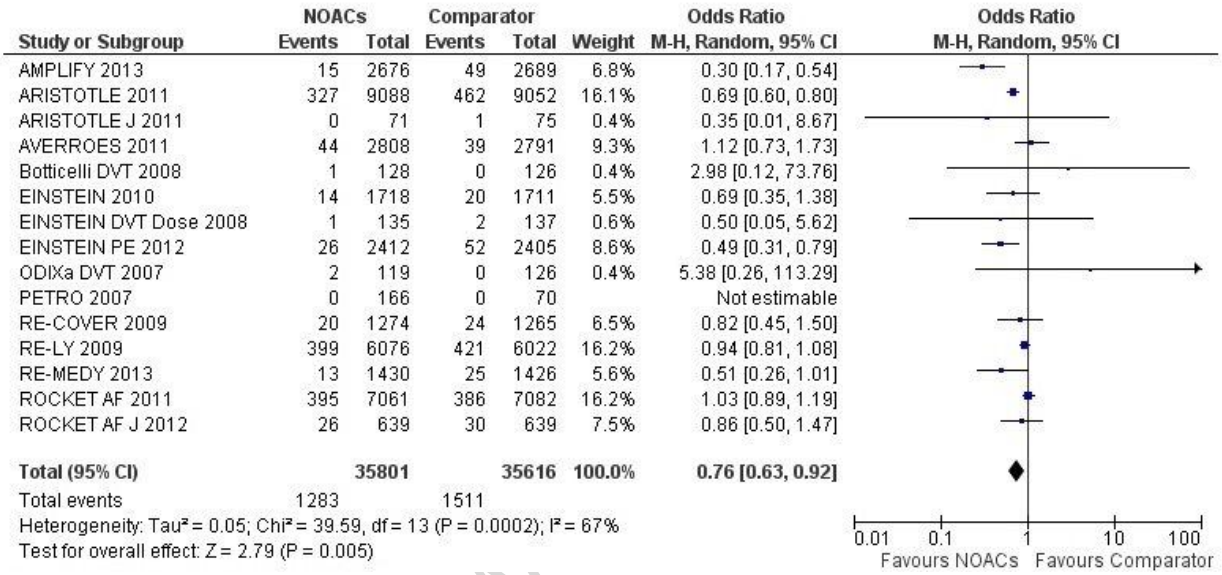

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Fig. 4

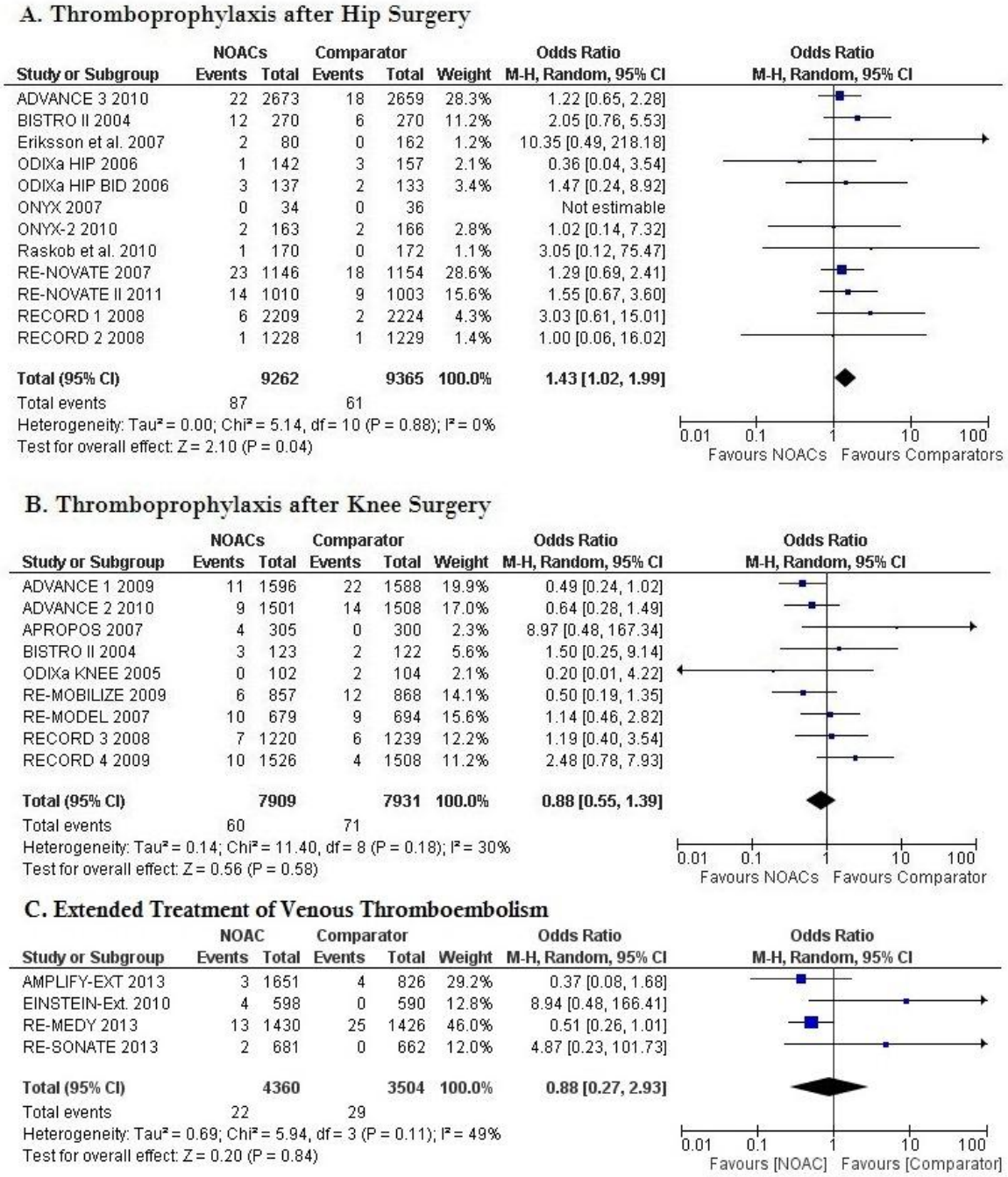

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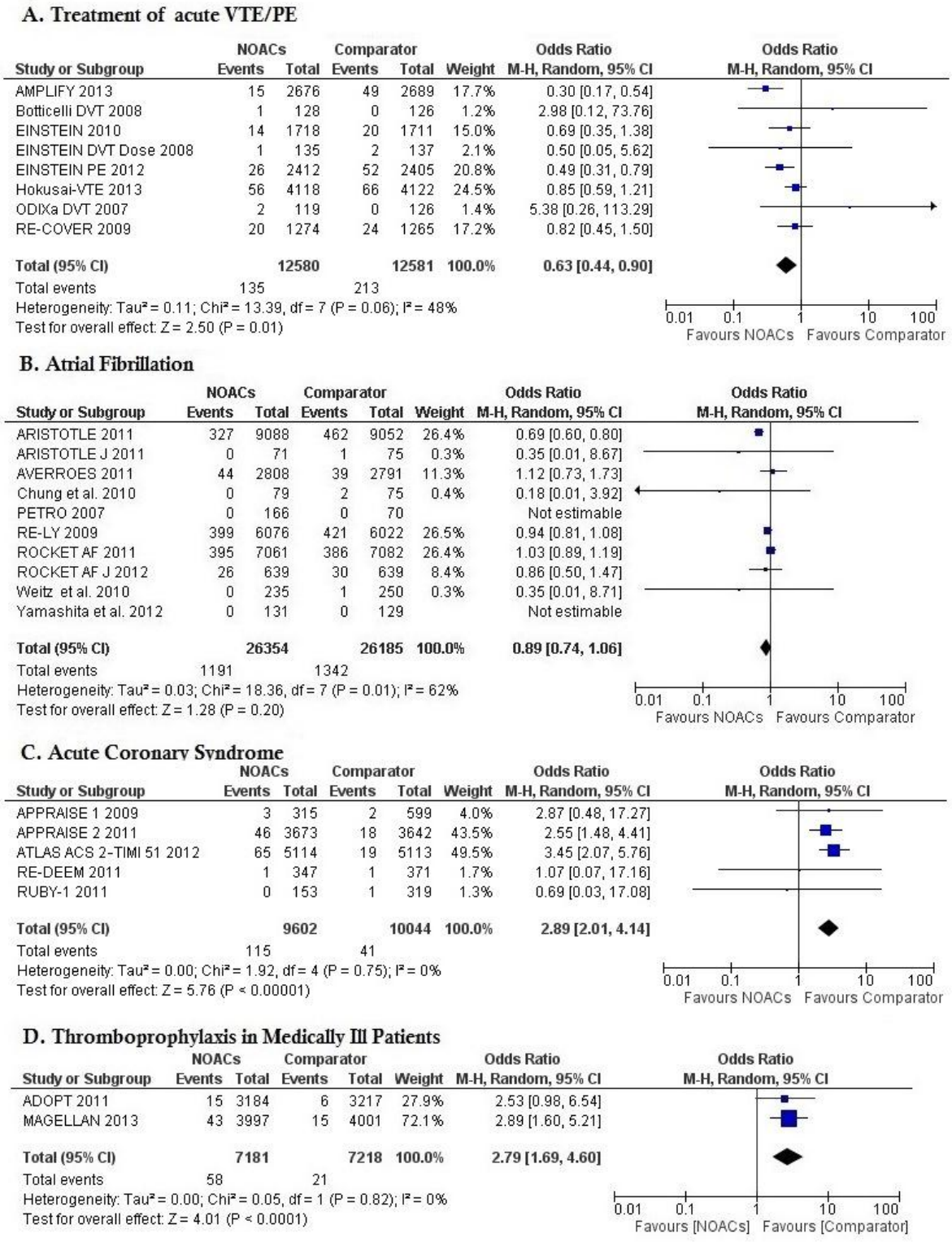
Fig. 5



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Highlights

- We performed a meta-analysis to evaluate the risk of major bleeding with the use of New Oral Anticoagulants (NOACs).
- Risk of major bleeding with new oral anticoagulants varies with their indication for use.
- NOAC may increase the risk of major bleeding after hip surgery, acute coronary syndrome and acute medically ill patients; but may be associated with less bleeding in treatment of acute venous thromboembolism or pulmonary embolism.

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